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The role of Oxalobacter formigenes in calcium oxalate stone disease

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Abstract

Calcium oxalate is the major component of about 75% of all urinary stones. Hyperoxaluria is a primary risk factor for calcium oxalate stone formation. The bioavailability of ingested oxalate and the extent of intestinal absorption of dietary oxalate are considered to be important factors in hyperoxaluria. *Oxalobacter formigenes* is a Gram-negative anaerobic bacterium that colonizes the intestinal tract. It is unique in that it requires oxalate both as an energy and carbon source. The only known factor which reduces colonization with *O. formigenes* is the treatment with antibiotics to which the bacterium has been reported to be sensitive. A deficiency of oxalate degradation by *O. formigenes* may increase urinary oxalate excretion, attributed to decreased intestinal oxalate degradation, leaving more oxalate available for absorption at a constant intestinal absorption rate. A lack of colonization with *O. formigenes* increases the risk of recurrent calcium oxalate stone formation. While evidence is emerging that orally administered *O. formigenes* can reduce urinary and plasma oxalate, the possible treatment with a probiotic still remains a challenge.

Keywords: calcium, oxalate, urinary stones, Oxalobacter formigenes, probiotic

Summary of recommendations

1. Colonization with *O. formigenes* is associated with a reduced risk of calcium oxalate stone formation probably resulting from a decreased excretion of urinary oxalate (GoR B)
2. Several studies have suggested that colonization with *O. formigenes* is markedly affected by use of antibiotics to which the bacterium is sensitive (GoR B).
3. Long-term controlled studies on the treatment of idiopathic calcium oxalate stone formers with *O. formigenes* are lacking so far.

1 Introduction

Calcium oxalate is the most common stone constituent, and is suggested to be the major mineral in about 75% of all urinary stones [1]. Hyperoxaluria is a primary risk factor for calcium oxalate stone formation. Since the molar oxalate-to-calcium ratio is normally at 1:10, even slight changes in urinary oxalate concentration exert much larger effects on crystallization and stone formation than comparable changes in the calcium concentration [2].

Hyperoxaluria can result from a high dietary oxalate intake, intestinal hyperabsorption of oxalate from the diet, or an increased endogenous production of oxalate from ingested or metabolically-generated precursors. The amount of oxalate excreted in urine has a significant impact on calcium oxalate supersaturation and stone formation. It has been suggested that dietary oxalate contributes up to 50% to urinary oxalate excretion [3]. The bioavailability of ingested oxalate and the extent of absorption of dietary oxalate may be important factors in hyperoxaluria.

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A high dietary oxalate intake plays a key role in idiopathic hyperoxaluria. Some foods, particularly vegetables, cereals and nuts such as sesame, almonds, wheat bran, mangold, rhubarb, sorrel and spinach, are known to contain high oxalate concentrations [4], [5], [6]. Among beverages, green and black teas as well as various vegetable juices were found to contain considerable amounts of highly bioavailable, soluble oxalate [4], [7], [8]. A high dietary intake of oxalate can significantly increase urinary oxalate excretion even in healthy individuals without disturbances in oxalate metabolism [9].

Intestinal hyperabsorption of oxalate can considerably contribute to urinary oxalate, even in the absence of gastrointestinal disorders. A study using the standardized [$^{13}C_2$] oxalate absorption test revealed a significantly higher mean intestinal oxalate absorption in idiopathic calcium oxalate stone formers (10.2%) compared to healthy controls (8.0%) [10]. However, the reason for this difference is unclear. Intestinal oxalate absorption greater than 10% was found in only 28% of healthy subjects, but in 46% of patients. Oxalate absorption greater than 20% only occurred in stone formers.

2 Methods

A systematic literature search was performed in PubMed over the last 40 years using the following key word: *Oxalobacter/formigenes.* Search results were limited to studies written in the English language. A total of 176 publications were identified, which were screened by title and, when appropriate, abstract. After exclusion of duplicates, a total of twenty-two were included in the analysis. It should be stated that there are no meta-analyses for *Oxalobacter formigenes* published in the literature. The studies were rated according to the level of evidence (LoE) and the grade of recommendation (GoR) using ICUD standards.

3 Results

3.1 Oxalobacter formigenes

Oxalobacter formigenes is a Gram-negative anaerobic bacterium that colonizes the intestinal tract of humans [11]. It is unique in that it requires oxalate both as an energy and carbon source. There is very little known about the biology of the organism, particularly on how it establishes and maintains gut colonization.

The only known factor which reduces colonization with *Oxalobacter formigenes* is the treatment with antibiotics. Several studies have suggested that colonization with *O. formigenes* is markedly affected by use of antibiotics [12], [13], [14], [15], [16], [17], [18]. In a study of 37 idiopathic calcium oxalate stone formers, only 11 (30%) tested positive for *O. formigenes*, whereas 26 (70%) tested negative [19]. Analysis of a history of use of antibiotics revealed that only 13% of *O. formigenes*-positive patients had taken antibiotics, whereas 81% of *O. formigenes*-negative patients had received antibiotic treatment before the start of the study. *O. formigenes* has been reported to be sensitive to a variety of antibiotics commonly used in clinical practice for the treatment of a broad range of infections [13], [15], [18]. These antibiotics include macrolides, such as erythromycin and clarithromycin, metronidazole, and doxycycline.

A prospective study in patients who where undergoing upper endoscopy and biopsy revealed that antibiotics for *Helicobacter pylori* infection leads to persistently reduced intestinal colonization rates with *O. formigenes* [15]. The absence of *O. formigenes* colonization in women could be attributed to frequent use of antibiotics owing to recurrent urinary tract infections, which have been found to be associated with increased oxalate excretion [20]. According to a recent study, the relatively lower rate of *O. formigenes* detection in relation to other populations outside the United States provides further evidence to support a general trend of the disappearance of this organism with socioeconomic development, likely due to higher general use of antibiotics within these populations [21]. A lack of colonization with *O. formigenes* increases the risk of recurrent calcium oxalate stone formation [16], [17], [19], [22], [23], [24], [25].

3.2 Oxalobacter formigenes and urinary oxalate excretion

The lasting elimination of *O. formigenes* could lead to a reduced rate or deficiency of oxalate degradation in the colon [16]. Oxalate degradation by *O. formigenes* might be expected to reduce the extent of urinary oxalate excretion. Whereas several studies have linked the absence of *O. formigenes* to higher urinary oxalate excretion [12], [23], [24], [26], others revealed no significant difference in urinary oxalate excretion between patients who tested positive or negative for *O. formigenes* [17], [27]. However, a major limitation is that none of these studies in stone formers were conducted under controlled conditions. A study in calcium oxalate stone formers on two days under controlled, standardized diet revealed that mean urinary oxalate excretion was significantly lower in *O. formigenes*-positive patients (0.318 and 0.367 mmol/24h, respectively) than in those who were *O. formigenes*-negative (0.454 and 0.474 mmol/24h, respectively) (p=0.003 and p=0.043, respectively) [19].

3.3 Oxalobacter formigenes and intestinal oxalate absorption

The understanding of the role of *O. formigenes* in oxalate metabolism is still limited. It has been hypothesized that the absence of this bacterium could be associated with higher intestinal oxalate absorption [16], [28], [29]. In our study in 37 idiopathic calcium oxalate stone formers, no difference in mean oxalate absorption, measured by [$^{13}C_2$]oxalate absorption test, was observed between *O. formigenes* colonized and noncolonized patients [19]. Intestinal oxalate absorption was 11.5±4.6% in *O. formigenes*-positive patients and 11.3±5.9% in *O. formigenes*-negative patients, which is consistent with mean intestinal absorption of 10.2±5.2% in 120 recurrent idiopathic calcium oxalate stone formers [10], [19]. Similarly, Knight et al. (2011) reported in 38 calcium oxalate stone formers that absorption was not significantly different in colonized and noncolonized subjects [27]. Overall, these findings suggest that intestinal oxalate absorption is not modulated by *O. formigenes*.

3.4 Oxalobacter formigenes and enteric oxalate secretion

There is still a significant lack of knowledge on the mechanism of action of *O. formigenes* colonization in patients with idiopathic calcium oxalate stone disease. The only study investigating the effect of colonization with *O. formigenes* on plasma oxalate concentration in idiopathic stone patients revealed that mean plasma oxalate concentration was more than threefold higher in patients without *O. formigenes* (5.79 µmol/l) than in colonized stone formers (1.70 µmol/l) [19]. While glomerular filtration rate was similar in both groups, the results of the study suggest that differences in urinary oxalate excretion were not apparently associated with either changes in glomerular filtration or tubular secretion of oxalate.

A hypothetical explanation for the higher plasma oxalate concentration in noncolonized stone formers is that the absence of *O. formigenes* is attributable to altered intestinal oxalate transport. Rat models have suggested that *Oxalobacter*, in addition to degrading dietary sources of oxalate, interacts physiologically with colonic mucosa by inducing active secretion of endogenously produced oxalate [30]. Hatch et al. (2006) demonstrated that this bacterial-enterocyte interaction results in a significant reduction in urinary oxalate excretion owing to this enteric oxalate shunt [30]. The latter study was also the first to demonstrate that endogenously derived oxalate can sustain *O. formigenes* colonization. In patients with primary hyperoxaluria, oral administration of *O. formigenes* has been shown to significantly induce enteric oxalate secretion, possibly by contributing to a transepithelial gradient favoring intestinal secretion of endogenous oxalate [31], [32].

3.5 Treatment with Oxalobacter formigenes

Results of clinical trials on the use of *O. formigenes* as a probiotic to reduce urinary oxalate excretion are inconsistent. Despite favorable results in a pilot study [31], the efficacy of orally administered *O. formigenes* for reducing urinary oxalate excretion could not be confirmed in a multicenter trial in 42 patients with primary hyperoxaluria [33]. In contrast, a recent study in 80 calcium oxalate stone formers randomized to receive either KMgCit or *O. formigenes* preparation revealed that the incidence of hyperoxaluria decreased at 1 month compared to baseline in both groups, while other urinary metabolic abnormalities remained similar [34]. However, the possible use of *O. formigenes* as a probiotic therapy remains a challenge with several hurdles to overcome before reaching clinical practice [35]. The main limitation of the use of *O. formigenes* is that its effect remains as long as the preparation is taken, indicating only transient gut colonization [31], [35].

4 Further research

Further studies with larger sample sizes are needed to define the exact role of *O. formigenes* colonization in calcium oxalate stone disease and to evaluate the efficacy of *O. formigenes* during long-term treatment.

5 Conclusions

Colonization with *O. formigenes* is associated with a reduced risk of calcium oxalate stone formation. Recent findings revealed that colonization with *O. formigenes* may reduce urinary oxalate excretion, attributed to increased intestinal oxalate degradation, leaving less oxalate available for absorption at a constant intestinal absorption rate. The observation that active enteric secretion of endogenously produced oxalate may be induced or enhanced by *O. formigenes*, thereby decreasing plasma oxalate concentration, may have important consequences for future hyperoxalemia treatment strategies. However, colonization with *O. formigenes* may be markedly affected by use of antibiotics to which the bacterium is sensitive. While evidence is emerging that orally administered *O. formigenes* can reduce urinary and plasma oxalate, the possible treatment with a probiotic still remains a challenge. Because only transient gut colonization with *O. formigenes* has been achieved so far, attention should be focused also on additional oxalate-degrading microorganisms such as *Lactobacillus* and *Bifidobacterium* strains and oxalate-degrading enzymes.

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